On page 89, line 24, after "CO_2H", insert --SEQ ID NO:16--.
On page 90, line 24, after "CO_2H", insert --SEQ ID NO:16--.
On page 93, line 6, after "$CONH_2$", insert --SEQ ID NO:17--.
On page 93, line 19, after "$CONH_2$", insert --SEQ ID NO:18--.
On page 93, line 26, after "$CONH_2$", insert --SEQ ID NO:19--.
On page 113, line 26, after "$CONH_2$", insert --SEQ ID NO:19--.
On page 133, line 3, after "leucine-alanine", insert --SEQ ID NO:20--.
On page 133, line 6, after "amide", insert --SEQ ID NO:21--.
On page 140, line 16, after "P-A-K-S-A-P-A-P-K-K-)", insert --SEQ ID NO:22--.
On page 140, line 20, after "NH2)", insert --SEQ ID NO:23--.

In The Claims:

Please cancel claims 1 to 43.

CRFE entered into date base on 7/30/01

Please add the following new claims:

--44. A method of making a non-immunogenic construct comprising at least two copies of an epitope of a T-dependent antigen bound to a pharmaceutically acceptable non-immunogenic carrier, which copies bind to a B cell membrane immunoglobulin receptor specific for the epitope but fail to form an immunon, comprising

(a) providing a non-immunogenic soluble carrier that has been subjected to a preparative sizing technique to remove substantially most high molecular weight non-immunogenic soluble carrier molecules and an epitope molecule of a T-dependent antigen;

(b) coupling two or more of the epitope molecules to the size-fractionated non-immunogenic soluble carrier to yield a conjugate preparation, thereby yielding a non-immunogenic construct which is free of high molecular weight immunostimulatory molecules.

45. The method of claim 44, wherein the epitope comprises a peptide epitope.

46. The method of claim 44, wherein the epitope comprises a carbohydrate epitope.

47. The method of claim 44, wherein the epitope comprises a nucleic acid.

48. The method of claim 47, wherein the nucleic acid comprises a phosphorothioate nucleic acid.

A2 cont'

49. The method of claim 44, wherein the epitope comprises a glycolipid epitope.

50. The method of claim 44, wherein the epitope is derived from an allergen.

51. The method of claim 44, wherein the epitope is derived from an autoimmune antigen.

52. The method of claim 44, wherein the non-immunogenic carrier comprises a dextran, a Ficoll, a carboxymethylcellulose, a polyvinyl alcohol, a synthetic polymer of D amino acids or a polyacrylamide.

53. The method of claim 52, wherein the synthetic polymer of D amino acids comprises a poly (D-GLU/D-LYS).

54. The method of claim 44, wherein the non-immunogenic carrier comprises a protein oligomer.

55. The method of claim 54, wherein the protein oligomer comprises an immunoglobulin or albumin.

56. The method of claim 44, wherein after the preparative sizing technique the size-fractionated non-immunogenic carrier has a molecular weight of less than about 100,000 daltons.

2 cont.

57. The method of claim 56, wherein after the preparative sizing technique the size-fractionated non-immunogenic carrier has a molecular weight of less than about 40,000 daltons.

58. The method of claim 57, wherein after the preparative sizing technique the size-fractionated non-immunogenic carrier has a molecular weight of less than about 20,000 daltons.

59. The method of claim 44, wherein the preparative sizing technique comprises size exclusion gel chromatography.

60. The method of claim 44, wherein the preparative sizing technique comprises ultrafiltration.

61. The method of claim 44, wherein the copies of the epitope are bound to the non-immunogenic carrier by a spacer molecule.

62. The method of claim 61, wherein the spacer molecule comprises an epsilon amino caproic acid or a delta amino valeric acid.

63. The method of claim 44, wherein the non-immunogenic construct comprises from about 4 to about 30 copies of the epitope.

64. The method of claim 63, wherein the non-immunogenic construct comprises from about 6 to about 14 copies of the epitope.

65. The method of claim 44, wherein the non-immunogenic construct comprises less than about 20 copies of the epitope.

66. The method of claim 44, wherein the non-immunogenic construct is immunosuppressive when administered in pharmacologically effective amounts.

67. The method of claim 66, wherein the non-immunogenic construct is immunosuppressive to T cells.

68. The method of claim 44, wherein the non-immunogenic construct is tolerogenic when administered in pharmacologically effective amounts.

69. A method of making a non-immunogenic construct comprising at least two copies of an epitope of a T-dependent antigen bound to a pharmaceutically acceptable non-immunogenic carrier, wherein construct-bound copies of the epitope are capable of binding to a B cell membrane immunoglobulin receptor specific for the epitope without forming a clustering of B cell membrane-bound receptors, the method comprising

(a) providing a preparation of a non-immunogenic soluble carrier, wherein substantially all high molecular weight non-immunogenic soluble carrier molecules have been removed from the preparation, and an epitope of a T-dependent antigen; and

(b) coupling the two or more copies of the epitope to the non-immunogenic soluble carrier to yield a non-immunogenic epitope-coupled construct.

70. A method of making a non-immunogenic epitope-coupled construct preparation comprising at least two copies of an epitope of a T-dependent antigen bound to a pharmaceutically acceptable non-immunogenic carrier, wherein at least two copies of construct-bound epitope are capable of binding to a B cell membrane immunoglobulin receptor specific for the epitope without forming a clustering of B cell membrane-bound receptors, the method comprising

(a) providing a soluble carrier and an epitope of a T-dependent antigen;

(b) coupling the two or more copies of said epitope to the soluble carrier; and,

(c) removing substantially all immunostimulatory molecules from the product of the reaction of step (b) to generate a non-immunogenic epitope-coupled construct preparation.

71. The method of claim 70, wherein the non-immunogenic epitope-coupled construct preparation has a molecular weight of less than about 100,000 daltons.

72. The method of claim 71, wherein the non-immunogenic epitope-coupled construct preparation has a molecular weight of less than about 40,000 daltons.

73. The method of claim 72, wherein the non-immunogenic epitope-coupled construct preparation has a molecular weight of less than about 20,000 daltons.

74. The method of claim 70, wherein substantially all immunostimulatory molecules are removed from the product of the reaction of step (b) by size exclusion gel chromatography.

75. The method of claim 70, wherein substantially all immunostimulatory molecules are removed from the product of the reaction of step (b) by ultrafiltration.

76. The method of claim 70, wherein the epitope comprises a phosphorothioate nucleic acid.

77. The method of claim 70, wherein the epitope is derived from an allergen.

78. The method of claim 70, wherein the epitope is derived from an autoimmune antigen.

79. The method of claim 70, wherein the non-immunogenic carrier comprises a polyvinyl alcohol, a synthetic polymer of D amino acids or a polyacrylamide.

80. The method of claim 70, wherein the copies of the epitope are bound to the carrier by a spacer molecule, wherein the spacer molecule comprises an epsilon amino caproic acid or a delta amino valeric acid.

81. The method of claim 70, wherein the non-immunogenic epitope-coupled construct preparation comprises from about 4 to about 30 copies of the epitope.

82. The method of claim 81, wherein the non-immunogenic epitope-coupled construct preparation comprises from about 6 to about 14 copies of the epitope.

83. The method of claim 70, wherein the non-immunogenic epitope-coupled construct preparation comprises less than about 20 copies of the epitope.

84. The method of claim 70, wherein the non-immunogenic construct is immunosuppressive when administered in pharmacologically effective amounts.

85. The method of claim 70, wherein the non-immunogenic construct is immunosuppressive to T cells.

86. The method of claim 70, wherein the non-immunogenic construct is tolerogenic when administered in pharmacologically effective amounts.

87. A pharmaceutical composition comprising a non-immunogenic construct comprising at least two copies of an epitope of a T-dependent antigen bound to a pharmaceutically acceptable non-immunogenic carrier, wherein at least two copies of construct-bound epitope are capable of binding to a B cell membrane immunoglobulin receptor specific for the epitope without forming a clustering of B cell membrane-bound receptors.--

REMARKS

Status of the Claims

Before entry of the instant amendment, claims 1 to 43 are pending. In the instant amendment, claims 1 to 43 are canceled and new claims 44 to 87 are added.